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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ALLERGAN, INC.
2525 DUPONT DRIVE, T2-7H
IRVINE, CA 92612-1599

EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

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12/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,057	CHANG ET AL.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-54* is/are pending in the application.

4a) Of the above claim(s) *38-45,52 and 53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-37,46-51 and 54* is/are rejected.

7)☐ Claim(s) _ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 09/24/07
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114.

2. Acknowledgement is made of applicant's filing of remarks 09/24/07. Claims 1-37, 46-51 and 54 are currently pending for prosecution on the merits.

3. Applicant's arguments filed 09/27/07 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 13, 33-35, 46-50 and 54 rejected under 35 U.S.C. 102(b) as being anticipated by Lipari (US 4383992).This rejection is analogous to the previous O.A. mailed 04/27/07.

Lipari discloses a topical ophthalmic solution comprising steroids compounds such as 0.12% prednisolone such as prednisolone acetate, about 20% beta-cyclodextrin, about 0.5% hydroxypropylmethylcellulose that is useful for the treatment ocular inflammation (Example 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 2-12, 14-32, 36-37 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lipari (US 4383992) in view of Loftsson (US 5472954), and further in view of Shinohara (5998488).

The teaching of Lipari has been discussed in above 35 USC 102(b) rejection.

Loftsson teaches a method of improving solubility and stability of pharmaceutical actives including prednisolone or prednisone by delivering the pharmaceutical actives in an aqueous solution comprising cyclodextrin (i.e., hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin), water-soluble polymer (i.e., hydroxypropyl methylcellulose) and a lipophilic and/or water labile active ingredient such as steroids (i.e., prednisolone, prednisone and dexamethasone) and additives (i.e., buffers, preservatives, pH adjusting agents, chelating agent, etc...), wherein said solution is prepared in various dosage forms including ophthalmic formulation, preferably a sterile, isotonic, buffered aqueous solution (abstract; column 4, line thru column 5, line 50; column 6, line 29 thru column 7, line 43; column 9, line 38-39; column 13, line 65 thru column 14, line 25; column 19, lines 16-31; Example 11; claims 96-107, 109, 110 and 113).

Shinohara is being supplied as reference to demonstrate the routine knowledge in using secondary agents such as chelating agent EDTA, cyclodextrins (e.g., β-cyclodextrin or γ-cyclodextrin) and NaCl in eye drops or ophthalmic solution.

The teaching of Lipari differs from the claimed invention in the use of cyclodextrin derivatives such as hydroxypropyl-β-cyclodextrin and hydroxypropyl-γ-cyclodextrin and excipients such as preservative, tonicifying agent, buffers and chelating agent. To incorporate such teaching into the teaching of Lipari, would have been obvious in view of Loftsson who teaches the use of cyclodextrin (i.e., hydroxypropyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin) and water-soluble polymer (i.e., hydroxypropyl methylcellulose) in improving solubility and stability of steroid drug such as prednisolone and Shinohara who teaches the

routine knowledge in using secondary agents such as EDTA and tonicifying agent such as NaCl in eye drops or ophthalmic solution.

It would have been obvious to one having ordinary skill in the art at the time of the invention was made to prepare the above taught composition in the effective amounts taught by applicant for with a reasonable expectation of success having above-cited references in combination. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to the specific pH range of the claimed composition, generally differences in an concentration or pH range will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such pH range are critical. Where the general conditions of a claim are disclosed in the prior art (especially ophthalmic preparation art), it is not inventive to discover the optimum or workable pH range by routine experimentation.

Response to Arguments

6. Applicant's argument in the response takes the similar position as to the amendment/remarks filed 02/02/07 that Lipari does not teach a cyclodextrin derivative such as cyclodextrin that has been chemically modified, "wherein one or more of the free hydroxyl groups of α-, β- or γ- cyclodextrin is replaced by any other group".

This argument is not found persuasive. Unlike the applicant's argument, there is no indication in the claims that the required cyclodextrin derivative in the claims 1, 13, 33-35, 46-50

and 54 must be essentially "a compound or a mixture of compounds, wherein one or more of the free hydroxyl groups of α-, β- or γ- cyclodextrin is replaced by any other group". Rather, the claims require only "a water soluble cyclodextrin derivative" in which the referenced beta-cyclodextrin "metes and bounds" the instant "a water soluble cyclodextrin derivative". Thus, Lipari clearly anticipates the claimed invention in claims 1, 13, 33-35, 46-50 and 54.

In response to the applicant's argument that the Office did not consider the unexpected results presented in the specification, anticipation under 35 USC 102 with respect to claims 1, 13, 33-35, 46-50 and 54 is an essentially irrebuttable question of fact, wherein the court stated that anticipation "cannot be overcome by evidence of unexpected results or teachings away in the art". *In re Malagari, 499 F.2d 1289, 182 USPQ; In re Spada, 911 F.2d 705, 15 USPQ2d 1655 (Fed. Cir. 1990); In re Fracalossi, 681 F.2d 792, 215 USPQ 569 (CCPA 1982); In re Alternpohl, 500 F.2d 1151, 183 USPQ 38 (CCPA 1974); In re Wiggins, 488 F.2d 538, 179 USPQ 421 (CCPA 1973); In re Wilder, 429 F.2d 447, 166 USPQ 545 (CCPA 1970).* Indeed, a reference might reside in a nonanalogous art and yet constitute an anticipation of a claimed invention under 35 USC 102. *In re Self, 571 F.2d 134, 213 USPQ 1 (CCPA 1982).* Thus, Lipari's topical ophthalmic solution comprising 0.12% prednisolone such as prednisolone acetate, about 20% beta-cyclodextrin, about 0.5% hydroxypropylmethylcellulose clearly anticipates the claimed invention in claims 1, 13, 33-35, 46-50 and 54.

Applicant's argument in the response takes the position that the unexpected result of the instant composition containing prednisolone acetate and cyclodextrin derivative provided by the

applicant (figure 3), particularly "the control compound provides no detectable prednisolone to the vitreous humor", is not suggested or taught in the prior art.

Applicant's objective evidence or secondary consideration of showing unexpected result was carefully considered. To be persuasive, the showing of unexpected superiority must be commensurate in scope with the claimed invention, and it must compare the claimed invention with the closest example disclosed in the prior art. However, applicant fails to compare the claimed invention with the closest example disclosed in the prior art. For instance, if the key element in the instant invention involves a mixture of prednisolone acetate and cyclodextrin derivative, particularly hydroxypropyl-γ-cyclodextrin, and if the closest prior art includes examples of an aqueous topical ophthalmic preparation comprising prednisolone acetate and cyclodextrin derivative such as beta-cylcodextrin (Lipari's composition, see Example 1 or Claim 6 composition) and an aqueous solution comprising cyclodextrin derivatives and polymers and lipophilic and/or water labile drugs such as prednisolone (Loftsson's composition, for example Table 1 and Claims 68, 89 and 113), experiments should desirably be conducted comparing a prednisolone acetate and hydroxypropyl-γ-cyclodextrin composition with the prior art examples of a prednisolone acetate and beta-cyclodextrin taught and a prednisolone, cyclodextrin derivatives (i.e., hydroxypropyl-β-cyclodextrin, hydroxyethyl-β-cyclodextrin, hydroxypropyl-γ-cyclodextrin, hydroxyethyl-γ-cyclodextrin, etc...) and polymers (i.e., methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, etc...).

In response to the applicant's arguments that "any bioavailability enhancement attributed to cyclodextrin is due to the ability of cyclodextrin to get more drug into solution, and not to any

enhanced membrane permeability attributed to cyclodextrin or complexes between cyclodextrins and drugs", "in general, the natural CDS and their hydrophilic derivatives are only able to penetrate lipophilic biological membranes, such as the eye cornea, with considerable difficulty", "it is not likely that large hydrophilic CD molecules permeate into those lipophilic membranes" and "CD molecules will only permeate biological membranes with considerable difficulty", the examiner recognizes that those known problems or obstacles of cyclodextrins are taught or suggested to overcome by the addition of water-soluble polymer to aqueous drug formulations containing CD, for example corticosteroids such as dexamethasone (see pages 69-70 "the effects of polymers on cyclodextrin complexation and the availability of drugs in cyclodextrin complexes"; pages 74-75, "0.7% Dexamethasone eye drop solution"; and "Conclusions").

As discussed above, the entirety of Loftsson (USP 5472954) or Loftsson's article teaches or suggests the usefulness of combining cyclodextrin (i.e., hydroxypropy-β-cyclodextrin and hydroxypropyl-γ-cyclodextrin) with water-soluble polymer (i.e., hydroxypropyl methylcellulose) in improving the stability, solubility or bioavailability of the lipophilic and/or water labile active ingredient such as prednisolone, prednisone and dexamethasone while minimizing ophthalmic drug irritation. Thus, one would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

Conclusion

7. No Claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Brian Kwon
Primary Patent Examiner
AU 1614